The Evolution of the French Public Policy to Promote Biotech Innovation : The Case of Genomics

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ABSTRACT

European Biotechnology companies and public policy-makers face to a number of crucial problems related to the development of Biotechnology in Europe : European industrial competitiveness, the relative under-exploitation of the European science base in Biotechnology, poor technology transfer mechanisms and difficulties in starting 'spin-off' firms.
The aim of this paper on innovation in genomics and biomedical related biotechnologies is to study the relative impact of the different public policy in France compared to the action of the private non for profit sector. Public policies in favour of biotech have changed during the last ten years from a support of research in large firms to a support of SME's creation in biotech. At the same time, large non-for profit organisations such as CEPH (Human Polymorphism Research Center) and AFM (French Organisation Against Myopaty) create a new dynamic by initiating path breaking scientific and technical programmes. This new scientific space has been complementary to the public policy, but only to a certain extend.
By studying the co-ordination mechanisms between the different organisations (non for profit organisations, public authorities, public sector research, Biotech SMEs and large firms, especially in the biomedical sector), this paper shows that the existing contradiction between the different tools to encourage biotech economic development can explain the poor development of biotech sector in France in the last few years. It also shows that the situation is getting better the last two years, especially in terms of firms' creation.

Keywords : public policy, Biotechnology, innovation, R&D, SME

Biotechnology[1] is a set of key enabling technologies, which are now being applied in a wide range of industrial sectors. The development of biotechnologies is based on transformations in the organisation of scientific production which are related to several different dimensions that are now combining to determine their evolution: (1) The need for a multidisciplinary combination of knowledge and skills;

[1] The term *biotechnologies* is used here in the sense of the utilisation of molecules or living organisms for technologies with industrial applications and/or the development of technologies devoted to the study of living things.

(2) The increasing returns on the recourse to biotechnology knowledge, where the most recent discoveries do not replace the old ones but combine with and systematise them; (3) Changes in the production methods of biological science (automation, computerisation), which lead to an increasing methodological codification (catalogues) of biological elements, thus permitting responses to specific demands; and (4) The considerable connectiveness between knowledge base and a wide range of innovative industrial applications (agrochemical, pharmaceutical, or environmental), which are gradually coming to light.

Biotechnologies are rooted in the academic arena while interacting with the industrial arena. They thus constitute a crossroads between one world whose rationale is supposed to be the preservation of diversity and another whose rationale is standardisation. In economic terms, the systematisation of biological knowledge can permit very specialised supply zones to expand, generally through academic spin-offs, while also allowing industrial groups seeking economies of scale to homogenise their production through biology's "new direction". This tension between the tendency towards standardisation and a preservation of diversification (the research-biotechnologies-industry linkage) is controlled by the forms of interaction between public action schemes rooted in institutional frameworks and new configurations of players composed of laboratories, universities, facilities and firms, which may be organised in networks and/or physically localised. The shaping of institutional framework seems to be partially ineffective.

European biotechnology companies and public policy-makers are faced with a number of crucial issues related to the development of biotechnology in Europe and the construction of a single market in this area. These difficulties have been highlighted by several recent studies. They include a lack of European industrial competitiveness compared to the USA (L. Orsenigo, 1989), the relative under-exploitation of the European science base in biotechnology (M. A. Delooze and S. Ramani, 1999), poor technology transfer mechanisms and difficulties in launching 'spin-off' firms (J. Senker and M. Sharp, 1997; V. Walsh, J. Niosi and P. Mustar, 1995) and, lastly, the technology transfer mechanism between public labs and SMEs on the one hand and large firms and SMEs on the other (J. Senker and M. Sharp, 1997).

In this framework, SMEs play a key role: as it has been shown by Barley *et al.* (S. R. Barley, J. Freeman and R. C. Hybels, 1992) and Powell *et al.* (W. Powell and P. Bratley, 1992), biotech SMEs play an intermediary role between researchers who perform science base and who make the scientific discoveries, and large firms that have established production, commercialisation and distribution capabilities. SMEs are the one which are able to cope with the tension between the tendency towards standardisation and the needed diversity of the scientific production.

The aim of this paper on innovation in genomics and biomedical related biotechnologies is to study the relative performance of the different public policies in France compared to the action of the private non-for profit sector. Policy-making has recently supported development of the biotech sector by

encouraging start-ups and creating favourable environments such as incubators, a specialised stock exchange or technopoles.

By studying the coordination mechanisms between the different organisations (non-for profit organisations, public authorities, public sector research, biotech SMEs and large firms, especially in the biomedical sector), this paper shows that the existing contradiction between the different policy instruments to foster biotech economic development can explain the poor growth of biotech sector in France in the last few years. It also shows that the situation is getting better the last two years, especially in terms of firms' creation.

The paper is ordered as follow: the first section presents the industrial and scientific base of the France biotech sector. The second section emphasises the evolution of public policy and it analyses how public policy combines with the non-for profit sector evolution. The third section concludes on the respective effects of public policy and non-for profit sector strategies on the distribution of knowledge and know-how needed to promote biotech economic developments.

1. BIOTECHNOLOGY INDUSTRIAL AND ACADEMIC RESEARCH IN FRANCE

Life sciences R&D : mainly public for ag-biotech, mainly private for health biotech

The statistics in France do not isolate biotechnology. However, around 21,000 academics and 9,000 PhDs students are involved in research in life sciences. In the private sector, around 15,000 persons are working in R&D in the pharmaceutical sector in 1996 and 2,588 in the agricultural sector and 3,500 in agrofood sector.

The massive R&D budget held by public ministries must be counterbalanced by the poor links between public and private sectors. This fact has been clearly highlighted by the "Rapport Guillaume"[2] concerning the French system of innovation (Amable *et al.* 1997). Between 1987 and 1996, France's share in scientific publication world-wide has substantially increased (from 4.3% to 5.1%) while its share in the European patent system has decreased by one and a half percentage point. However, the specific situation of biotechnology is better than the general situation. Even if the share world wide patents for pharmaceutical products between 1990 and 1997 has decreased from 7.4% to 6.5%, the French European patent share has increased from 26.3% to 27.3% during the same period. Moreover, the biotech patent share was stable at the world level and increases from 17.4 to 19.0% at the European level. France has a good position in Europe for pharmaceutical products and a strong scientific base in agricultural and agrofood life science.

Table 1 reveals that, compare to the pharmaceutical sector in which private firm investments are important, the public sector R&D in agriculture and agrofood sectors is dominant. Taken as a whole, these sectors represent almost 3% of the Gross Domestic Product each and they employ more than 1.5

millions people compare to less than 1% of the GDP for the pharmaceutical sector. Public research appears to be very strong in pharmaceuticals compared to the private research workforce in agriculture and agrofood sectors.

Around 162,590 persons are working in R&D in the private sector. Amongst them, 68,487 are PhDs or engineers in 1996. 156,000 persons are working in public sector research (70,000 researchers). In the public sector, around 13,870 persons (6,000 PhDs) are working in human health sector and 11,000 in agriculture (3,163 PhDs).

Table 1 : The main figures of life sciences R&D (1997)

	Gross Domestic Product 1254 MEuros	Number of firms	Number of employees	Number of researchers	
				Public sector	Private sector
Agriculture	3 %				
Agrofood	2,35 %	3.257	1.677.400	11.317	6.087
Pharmaceuticals	0,8 %	271	87.700	13.874	17.960
Life sciences (other)				29.405	
Total				70.000	

Sources : INSEE, OST report 2000, MENRT 1999.

Even if general statistics do not exist in France on biotech research human resources, experts agree to characterise the French situation as a dual one. Government invests in ag-biotech research through universities and the national labs (mainly the National Institute for Agronomic Research - INRA, agricultural departments in engineer schools and the National Center for Scientific Research - CNRS) and pharmaceutical and human health research is mostly funded and performs at the firm level.

The linkages between science and innovation

Most existing comparative studies on industrial and science base rely on patent applications and publications to study the relative positions of the three major industrial regions, namely Europe, the United States and Japan. All these studies conclude of the poor European capabilities to transform science-based knowledge into valuable economic knowledge (patents). The lack of European industrial competitiveness compared to the USA has been pointed out. One of the explanations of this situation is the weak technology transfer mechanisms and difficulties in starting 'spin-off' firms, especially between public labs or large companies on the one hand and SMEs on the other.

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2 Guillaume, H. (1998) « Rapport de mission sur la technologie et l'innovation »

However, such analyses, though more convenient for international comparison, do not take into account that Europe comprises heterogeneous countries. These heterogeneities are particularly relevant where public policy and institutional environment are under study. Delooze and Ramani (M.A. Delooze and S. Ramani, 1999) assess the specific characteristics of the three European major countries in biotechnology : France, Germany and United Kingdom.

Using Derwent Biotechnology Abstract on patents and publications, they show that France appears to have a weaker position than Germany and UK. However, even if Germany and UK have about 40% more publications than France during the period, the ratio publications on patents indicates that there is no significant differences between in the efficiency with which scientific knowledge is transformed into innovations (table 2).

Table 2 : Relative positions of France, Germany and United Kingdom

92-95 DBA patents	France	Germany	United Kingdom
Total number of patents	578	1013	946
Ratio of publications to patent applications	3.2	3	3.3
No. of organisations involved	209	554	376
% of organisations that are public labs	30.1	11.9	30.6
% of organisations that are private companies	56.0	45.8	55.3
% of organisations that are individuals	13.9	42.2	14.1

Source : Delooze, Ramani, 1999 (adapted).

When they look at the patent depositor profiles, Delooze and Ramani identify the specific characteristics of countries: (1) Germany tends to seek domestic protection (only 13% are extended at the European and world level) contrary to France and UK which are extended at the world level for 81% of them in UK and 52% in France. In France and UK, public labs are more active than in Germany in patent deposit. They also show that large depositors (organisations that fill more than 5 patents during the period) are more concentrated in UK and Germany than in France.

Joly and Delooze (P. B. Joly and M. A. Delooze, 1999) show that biotech SMEs are more likely to co-patent than large firms. The phenomenon of co-deposit is not prevalent in the three countries studied. It can reveal that the patent science base mainly comes from internal R&D and not from collaborative research.

Studying the science and technological base of a country through patents has two limitations: (1) a patent application is a signal of technological competencies but its economic value depends on the capacity of the innovating firm to exploit the patent and to generate revenues through it. (2) the propensity of patenting is different from one technological field to another and from one economic sector to another. Lemarié *et al.* (S. Lemarié, M. A. Delooze and V. Mangematin, 2000) show that the technological map of a country differs if the mapping is based on patent analysis and on technological competencies reported by firms.

However, four lessons can be drawn from these studies: (1) The three countries present a similar profile in terms of the efficiency of transformation of scientific knowledge into innovation, even if the number of patents differs. (2) Differences do exist between European countries in terms of division of work amongst actors involved in science and technological production in biotechnology. These differences can be related to the public policy in favour of biotechnology. (3) The differences in co-patenting between large firms and SMEs show that companies have different profiles of collaboration according their size. Thus, the effects of the public policy will be different if it relies on large firms or on SMEs. (4) This study of co-patenting shows the central role of SMEs in the development of biotechnology as a nexus of interorganisational collaboration between SMEs and large firms. Analysing the international recent trends in knowledge creation and appropriation in genomics, Delooze *et al.* (M. A. Delooze, R. Coronini and P. B. Joly, 2000) show that all these conclusions can be applied in the specific case of genomics. Performance to transform basic research into industrial applications is weaker in Europe than in United States and Japan. This particular situation pleads for a specific intervention of public authorities to reinforce the European potential in genomics. Public labs have a central role to play in technology transfer, especially in the pharmaceutical and agriculture sectors. Japan tends to rely on competence in technological development and the production of mass data, areas in which Japanese firms excel.

II. EVOLUTION OF POLICY AND SUPPORTS IN FAVOUR OF GENOMICS

The last ten years have been characterised by a growing importance of the non-for profit sector in biotech research funding while the targeted actors for the public support in favour of biotech have changed from large firms to SMEs. After a short presentation of these evolutions, the coherence of the two actions will be analysed.

The emergence of new actors and the evolution of public policy

An original feature of French medical research relative to the general organisation of the country's scientific research is the role of non-for profit sector (charities) which mobilise private resources (e.g., for the Institut Pasteur or the Institut Curie) (Branciard, 1999). Their presence serves to modify the institutional scientific framework as defined by public authorities. In this context, genomics, emerging from a new techno-scientific field based on genetic engineering and biotechnologies, was the fruit of the decisive impetus of two private structures, the *Centre d'Etudes sur le Polymorphisme Humain* (Centre for Research on Human Polymorphism, CEPH) and the *Association Française contre les Myopathies* (French Neuromuscular Distrophy Association, AFM).

The CEPH was a private laboratory set up by a foundation in 1983; as such, it defined its own rules of operation and personnel hiring, but as of 1988, it was funded by a direct budget line from the Ministry of Research. From an *organisational* standpoint, the CEPH constitutes a double breakthrough. In

terms of research, it breaks with the handcraft practices of French research teams. Its investment in a massive, technological, semi-industrial approach depends on funding for operations and equipment that is three to four times higher than that of a classic laboratory of the same size. From the *management* standpoint, its private status, which allows it to hire personnel without the constraints faced by public institutions like INSERM or the CNRS, make it an atypical structure enjoying research conditions close to those prevailing in the United States. *From the standpoint of the micro-foundations of the technological evolution of sequencing,* which extends to its present industrialisation, this double feature allowed the CEPH to situate itself in an essential segment.

The AFM is a non-for profit organisation founded in 1958 to work for the curing of hereditary neuromuscular diseases. AFM's activities fall into three domains: collection and management of funds, assistance to individuals, and scientific research. In 1987, observing the relative inadequacies of the State concerning research on genetic diseases, AFM decided to provide financial support in this area. Since 1988, its scientific policy has covered the entire spectrum, from clinical to therapeutic to genetic research, with a combination of long- and short-term projects, exploration and application, in short, every activity likely to contribute to the development of treatments. Along with its scientific programmes, the AFM's laboratory, the Généthon, had two development programmes in computer science and technology.

United by common interests, the joint activities of the CEPH and the AFM set out the main significant parameters of genomics in France, a crossroads between academic research and industrial applications, and related biotechnologies. Their appeal to the public authorities to create a dynamic by initiating path-breaking scientific or technical programmes perpetuated this existence and gave rise to the main dimensions of a **new scientific and technical space** permitting complementary interventions by the public authorities, public and private research bodies, industries and hospital institutions. In 1992, Généthon's publication of the physical and genetic maps of the human genome placed French genomics in the forefront in face of international competition. The success of genomics through the initiatives of the AFM, "government partner," led the public authorities to take over for the association on issues that the latter considered to be of collective interest, such as the localisation and identification of genes, and to follow in its footsteps by investing heavily in mapping and sequencing.

The AFM's schemes contributed more to creating a research field that was well endowed financially and technologically and that brought together different skills around genomics than to shifting the orientations of public research. They initiate the technology platform policy and thus exerted a "lever effect" on the existing scientific structure, mobilising a high-level academic potential and giving rise to a technological potential for research with rapid applicability, thus creating a competitive advantage.

At the beginning of the 1980s, the objective of the French public support for biotech was dedicated to encourage a number of industrial sectors such as agrofood and seeds. In this way, public funding was

used to revitalise groups working in the life sciences and bring them together, at the same time assisting them to rapidly integrate molecular biology and genetic engineering methodologies. The main mean was to encourage collaborative research between public sector research and large firms. At the beginning of the 1990s, the authorities decided to directly support the big industrial groups' research and development programmes, so as to accelerate the commercialisation of research through concrete action. But, in 1996, both the aims and the economic tools of public policy in favour of biotechnology changed. It aimed to reinforce the partnership between private and public research, and also to encourage the creation of new growth companies by facilitating research scientists' mobility between the sectors (P. Monsan, 2000). This was a strong incentive to business creation, and at the time was backed up by renewed interest in biotechnology from the finance community, in particular for gene therapy, neuro-degenerative disease treatment and genomics. The same year saw the arrival of the EASDAQ (European Association of Securities Dealers Automated Quotation), European financial market for high growth high-tech companies, together with that of the Paris Bourse's New Market, both factors contributing to the development of numerous biotech company creation projects. The national public policy in favour of firms' creation has been reinforced by the public policy of regional authorities, which aim to create wealth and jobs in their region. Thus, incubators and scientific parks have been set in different regions in the late 1990s. Even if these tools are not dedicated to biotechnologies, they all encourage SMEs creation.

Co-ordination mechanisms between public research bodies: scientific and technical dynamics and institutional inertia

The CEPH and Généthon had opened up a scientific field by means of one technology, massive sequencing; the public co-ordinating mechanism was responsible for anchoring this technology in a specific context (a segmented scientific community) by creating an institutional framework structuring this community around shared objectives.

Public policy at the state level took multiple forms. In addition to the traditional tools such as subsidies and research contracts, the public authorities set up the *Groupement de Recherches et d'Etudes sur les Génômes* (Genome Research Group, GREG), which was given the double responsibility of distributing public resources and developing forms of supervision for the scientific and technical activity. Created in 1993, the GREG does not resist more than 5 years to the scientific (and governmental) cleavages around the genomic strategy (whether or not to join the international genome programme, cleavages amongst institutions, etc.).

The effort at structuring and co-ordinating the genomics research community focused on the development of technological advances in the area of systematic analysis of DNA and genomes (automation, identification, marking, separation), the one of the bioinformatics services that are essential to genome research and training activities to improve the skills level of GREG's partners in bioinformatics and turn out researchers with double specialities in information science and genetics.

Through the resources allocated to it, GREG had the effect of displacing a certain number of teams towards a field between the genome and medical genetics, which gave them a respectable position internationally and allowed them to benefit from the consequences of Généthon's mapping and advances. It defined the contours of a scientific community at the intersection of fields of common interests, but this community remained fragmented, without co-operative ventures.

Until mid 1990s, the juxtaposition and simultaneity of the mechanisms for co-ordinating public activity with the AFM on the one hand and the GREG on the other gave rise to an institutional segmentation of scientific policies for the life sciences and the scientific field in biology between medical genetics and genome research, the effects of which were negative for both scientific co-operation and the creation of biotechnologies. The mechanisms for incentives and co-ordination did not function consistently enough to create common rules and norms that might provide public action guidelines for supervising collective scientific and technical activity. Institutional inertia and an uncertain legal environment thus encumbered the institutionalisation of a potentially innovative scientific and technical space.

The leading role of charities in bridging public labs and SMEs

As it was mentioned before, the aim of the public policy until mid 90's was to ensure the mobilisation of skills and means at the interface of life science and chemistry. The Bioavenir programme was set up between public labs and one industrial partner, Rhône-Poulenc, in order to accelerate the knowledge transfer from public research to industrial use. Taken as the whole, public policy did not encourage the creation of biotech start-ups during this period. The room opened by its absence was occupied at two levels : non-for profit association and local government.

AFM mobilises SMEs

As the strategy of AFM was to focus on gene therapy, it was necessary for the association to acquire an industrial backing capable of creating a market to make the large-scale development of these therapies viable. The AFM relied on a double strategy. On the one hand, it signed co-ordination agreements with biotechnologies firms, once it had organised concerted actions to generate innovation by combining specific complementary assets (with the AFM monitoring the patients' genes). For the small companies in biotechnologies, the contribution of the patients' associations provided an incentive to involve themselves the field of gene therapy, through long and costly investments, through the close collaboration with clinicians and the implementation of the therapy (the co-operation of the patients), through the co-ordination of complementary assets to bring together varied knowledge and know-how (setting up a technological basis, co-ordination of research centres in vectorology and gene therapy centres, etc.), which were subsequently to allow the companies to transfer acquired competencies on rare diseases in order to enter the sought-after mass markets. The AFM thus signed

agreements, first with Transgène, then Genset, and finally Rhône-Poulenc. This was to give rise to the problem of the private appropriation of externalities produced through co-operation: the AFM ultimately registered patents on the genetic disease genes discovered in order to protect the pharmaceutical industry's exploitation rights.

Furthermore, alongside its co-ordination activities intended to modify research practices, by initiating ties between research teams funded by the association and industry, relations which were to be perpetuated over time, the AFM sought to influence the public authorities so that the latter would attract to the field of gene therapies the industrial skills likely to create a favourable environment for them in terms of technological platforms and market.

Emergence of local authorities in biotech

In addition to the national policy (mainly research policy) in favour of biotechnology, new economic tools have been mobilised to support the development of biotechnology. These tools were first used at the regional level through the development of biopoles. To foster economic activities in their geographic area, regions supported firms' creation and created a supportive environment for the firms, which decided to settle in a specific area. More concretely, the local public authorities created specific funds to help entrepreneurs. The main tools are credit facilities, seed money at the beginning of the activity and free of charge buildings during a three years period. In some region like in Clermont Ferrand, local authorities set up local agency for advising start-ups.

To enhance their area, local governments use two kinds of incentives : first of all, they tend to reinforce communication and transportation means. Second, they tend to attract good scientific teams in local universities or research centres to create a scientific environment.

But with regard to its efficiency on the decade, in biotech in general and in genomics in particular, the French innovation system seems to be fragmented and partially inefficient until mid 1990s. The CEPH and AFM, which private structures, have played innovative roles by introducing semi-industrial scientific methods into molecular biology and developing molecular genetics. They have laid down the foundations for a new scientific and technical space and given France international standing in genomics. But there is a total lack of incentives in the French academic milieu to recognise interdisciplinary in the careers of researchers. Neither the GREG nor the biotech programmes play a central role for structuring a broader space around a clearly identified national genomics programme bringing science and industry into interaction.

Beyond the rhetoric developed by the S&T institutions about the opening up of research to the socio-economic players and the strengthening of industrial partnerships, the coherence in the interaction of French institutional arrangements for the development of ties between life sciences research and economic competitiveness, technological opportunities, creation of new activities and industrial development remains in a first time limited.

III. RECENT CHANGES IN PUBLIC POLICY AND ITS EFFECTS

Weak coherence of the national system of innovation in genomics and factors of its poor efficiency

At the beginning of the 1990s, the institutional environment in France was not then ready for supporting genomic research. Although the ethical laws[3] provide scientists with the legal environment, industrial property (patents) on genomics remains unclear until now. Thus, the organisation of closer interactions between public research and industry suffered from the problem of the **legal protection of biotechnical inventions** and the **patentability of the elements and products of the human body**, insofar as the latter constitute, for the moment, the essential source of "raw material" for biomedical research and industry. In the United States, the need to describe the new function of the genetic sequence claimed as an "invention" led to a maximum of anticipation, with requests for the protection of the widest possible range of potential applications. Definitively adopted in July 1998, the European directive concerning genome patenting should have been translated into the French legislation by July 2000. But problems of compatibility between European and French legislation occur.

The economic incentives of government action in France over the period studied seem to have been too little and too late to encourage co-operation by giving rise to the creation of small French enterprises, while regulations remained too cumbersome.

Two other characteristics of the environment need to be underlined. At the beginning of the 1990s, the financing system for biotech start-ups did not yet exist. The new market was set up in 1996 and the inadequate registering of patents by public research bodies with exclusive licenses for small enterprises refrains venture capital investments. In fact, venture capitalists only invest in patented technologies. The second feature was the absence of mobility of academics from public research to private firms, a rigid definition of the researcher's status, which excludes any shareholding in a start-up and would create difficult conditions of return to the original public research institution. Thus, t*he creation of businesses has remained slight*, while biotechnology is a sector where innovation emerges above all from small companies, whose creation is closely tied to the institutional system. In terms of performance, Europe's lag in 1996 relative to the United States in the area of biotechnologies companies was patent (716 companies, employing 27,500 individuals, compared to 1,287 in the United States with 118,000 employees, according to Ernst & Young, 2000), but the industry was getting off the ground. France, however, wound up in third place in 1997, behind Great Britain and Germany, countries where recent changes in legislation and the commitment of public authorities have given rise to the doubling of the number of companies every year since 1996. Several of the French ones have nevertheless risen to world rank (Genset, the first to have been rated on the new market and

[3] In addition to the biomedical legislation (1988 - Loi Huriet), France has three acts of ethics : respect of human body (moratoria on research on embryo selection, etc.); protection of privacy on medical data and experimentation on human.

NASDAQ in 1996, Cerep, Flamel Technologies, IDM, Appligène, Oncor, Transgène, Genopoïetic, Chemunex, Biovector Therapeutics).

The process of building this new field, genomics, thus remained fragmented, for lack of an institutional awareness that would have significantly changed the public authorities' forms of intervention. This sectoral public policy has in fact been marked by a "determinism" of institutions shaped to meet objectives defined by post-war scientific and technological policies (Callon and Foray 1998). Its "mission-oriented policy" (Ergas 1992), characterised by a centralisation of top-down decisions and a concentration of resource allocations on major programmes, has been juxtaposed with zones of non-decisions and dispersion over the new fields to develop in a science-innovation tandem. In addition, it has remained bound to the linear model of innovation that goes from basic research to applied research to the development of products or services. In the French industrial environment of the 1985-1996 period, it has thus generated low efficiency relative to the stakes of the mechanisms intended to produce, distribute and exchange new knowledge and skills.

SMEs development, researchers mobility and distribution of knowledge

The development of biotechnology industry has been characterised by the development of biotech SMEs. Powell *et al.* (W. Powell and P. Bratley, 1992) attribute this development to the fact that biotechnology is a competence destroying innovation for established firms in client industries like pharmaceuticals or chemicals. Lacking of investing in biotechnology, the large firms channel their investments in biotech through research contracts with universities or public labs and through forming joint ventures to obtain complementary assets or competencies. Consequently, the biotech industry is characterised by a network structure of interorganisational alliances that govern the exchange of complementary assets and competencies among SMEs, scientists and established firms.

By formulating policies and programmes encouraging strategic alliances between companies and research organisations, the creation of spin-off firms, the implantation of R&D structures transcending traditional institutional borders (public-private, academic-applied, etc.), the founding of scientific and industrial concentrations at the local level, and so on, the public interventions would follow a rationale aimed at the organised accumulation of knowledge and the creation of capacities for innovation.

Translation of this model into public policy action

The discourses related to this model were linked to expanding practices of research production that were nonetheless tied to the institutional context of the United States. These practices were transformed into a normative system on the basis of the shared representations made by the institutional players, and it was then drawn upon in order to create new shared socio-cognitive guidelines for public action, as criteria for updated forms of action but with different kinds of

appropriation depending on the European countries involved. It was spread largely through experts' reports and programme activities, mainly those of the European Commission. Interaction with R&D at international level and competition/co-operation with other systems of research and innovation gave rise, at the European level, to the diffusion of scientific advances and techniques, the standardisation of tools and procedures, the modification of guidelines for the science-innovation relationship and the aligning of European intellectual property law with American law in the biotechnologies field. Beyond stimulating the dissemination of knowledge between member countries, these policies tend in fact towards effects of normalisation in the production of knowledge and the creation of technological and organisational standards that can be linked to the diffusion of the updated "model" of the mode of production of research at work in the biotechnologies.

Given the considerable volume of funding provided by the European programmes relative to French budgets for research or technological development outside the major programmes, the impetus provided by the European dynamic could help to restructure the functioning of public and private research in France. At the French level, the model was thus translated into several key actions both at the national and at the local levels :

Innovation promoting changes in the institutional environment

At the level of State action, a certain number of programmes and new measures, of general or particular scope, have permitted the introduction of new strategies for action by removing legal obstacles and created conditions for the development of small innovative enterprises through the shift from a patrimonial to an entrepreneurial rationale.

The law on innovation of July 1999 was explicitly aimed at bringing public research and companies closer together in order to "increase the capacity for innovation and the creation of wealth". It allows for several forms of incentives :

- The elimination of statutory restrictions on researchers' mobility, allowing them to create a company on the basis of their studies without definitively leaving public research, or to contribute their expertise or their participation in the capital of a company while maintaining their posts.
- The creation of structures favouring the emergence of innovative small enterprises, notably spin-offs from research institutions or universities; **incubators** offering an implantation site but also technical support and legal and financial advice (23 MEuros for 29 selected projects amongst which 8 bio-incubators, in 1999 and 2000); and **seed-capital funds** to facilitate the first stage of creation, with State funding leading to calls for projects (15 MEuros in 1999, the third to BioAm, the national fund for investment in biotech which would come to 30 MEuros with private partners); as well as a competition for aid in the creation of innovative technological enterprises (15 MEuros in 1999, for 244 selected projects a quarter of which in biotech; 30 MEuros in 2000, for 296 selected projects, 20% of which in biotech).

• The institution of a fiscal context favourable to subscription funds for shares in the creation of enterprises (BSPCE, employee profit sharing) and joint funds for investment in innovation in 1997 (FCPI). Before, the public funding for innovation in SMEs was 460 MEuros by year, as only 62 MEuros from the private sector. For their creation, the FCPI have raised about 185 MEuros. The tax system for stock options remains largely dissuasive, however.

• The inclusion of innovative small enterprises in a legal framework that is more appropriate to them: the simplified stock company (*société par actions simplifiée*, SAS), which facilitates calls for investors and venture capitalists.

In terms of the *financial system*, a positive change emerged with the creation of the New Market and EASDAQ, allowing high-tech companies to be rated on the stock market. This trend was accentuated by the State's creation of a public venture-capital fund (FCPR) of 140 MEuros, which, through the lever effect, allowed several times this amount to be raised amongst institutional investors, banks or local communities (615 MEuros in 1998).

A new technological policy for the biotechnologies: bridges between public research and biotechnologies

Since 1996, the life sciences and biotechnologies have been made priorities for governmental action, in order to strengthen France's position on a strategical issue for growth and employment. A second Biotechnologies Programme was undertaken for five years, with joint public-private funding of 140 MEuros following calls for proposals. Its objectives are to stimulate collaborations between public laboratories and SMEs, to aid in the development of innovative principles or procedures (with the goal of tripling the number of international patents registered by the French), to favour the emergence of several thousand SMEs in order to create four hundred stable high-tech companies and set up new biotechnologies sectors that create jobs.

In 1998, the Ministry of Research, which is empowered to intervene in industrial support for research, launched appeals to promote actions between public research and SMEs along two main lines: transfers in biotechnologies, where the large majority of the projects selected deal with health (genomics, diagnosis and gene and cell therapy), and health technologies (instrumentation, imaging, bioinformatics). In 1999, funding incentives were focused on programmes dealing with the extension of human genome sequencing and targeting therapeutic security and new treatments, functional genomics and biomaterials. The Ministry of Industry likewise launched a call for projects in "post-sequencing genomics" along three bio-industrial tracks related to predictive, preventive and therapeutic medicine and thus giving rise to a partnership between public research, small biotech industrialists providing technologies and services and applications CSBs.

Apart from incentive-providing grants, the State's impetus is now channelled in two main directions. The first involves the creation of genomics infrastructures: major facilities like the Centre National de Séquençage (which has a public budget of 12 MEuros for ten years), the Centre National de

Génotypage (7,7 MEuros annually), the Centre de Ressources Informatiques Infobiogen and the Centre de Ressources for DNA collections, along with the development of national networks of genomic bioinformatics and genopoles. The second involves umbrella research programmes.

The most state-led ministerial scheme for bringing together in one site research (public, private, industrial), small enterprises in the making, experienced SMEs, industry and the university is the genopole for genomics and biotechnologies implanted in Evry in 1998. The idea is to develop a European-level pole of some sixty biotechnologies companies around the massive facilities of the CNS, CNG, and AFM laboratories by drawing on the results of public research, the installation of new companies in incubators and the synergy amongst research, technological platforms and industry. The project enjoys support from the major public players (State, public S&T institutions) and regional and local authorities, as well as the presence of experienced private players such as the AFM, Genset and Aventis.

It is clear that the structural elements of the national system of innovation have been modified and that new schemes of public intervention, inspired by "diffusion-oriented policy" in their principles, aim to meet the new historical objectives by completing the Colbertist model with more diversified and decentralised conditions of innovation spread throughout the economic and social fabric. Through the multiplication of partnerships, these allow for different fields of application (agricultural and agro-industrial, pharmaceutical, medical, environmental) where the generic products of genomic research can be accommodated. They also seek to favour the strategy of incentives over that of grants in order to reinforce the fluidity of the science-industry relationship in the configuration of players relative to the public authorities-industry relationship.

In addition to the national level of public action, several local initiatives have been carried out during the last five years. The local governments create seed money to support the creation of *high tech* SMEs in their region. They also set up a favorable environment including technological facilities, advises services and local incubators.

These public policies seem to be more adapted with the innovation patterns in biotech in which knowledge creation is distributed and in which SMEs have a leading role for innovation.

A growing number of start ups

According to the survey conducted by Mangematin (V. Mangematin, 2000), On 1 January 1999 France had about 300 biotechnology SMEs employing 15,000 people, with an estimated turnover of 2000 MEuros[4]. Average size in terms of number of employees is about 40. Results show that just fewer than 70% of firms in the sample were created after 1990. One third of the biotech SMEs have been created since 1997, after the beginning of the new public policy. Firms that have existed for 20

[4] This figure does not take into account divisions in certain firms with over 500 employees, specialised in biotechnology.

years or more account for 12% of the sample, whereas more recent firms account for 69% of the total. Less than 20% of the firms were created between 1980 and 1990.

In France, development of the biotechnology sector remains concentrated on a few leading regions, which local public authorities created incubators, sciences parks or technological facilities. While Ile de France remains dominant, especially as regards firms created around universities and Genomic Valleys, Alsace, Auvergne, Aquitaine, Brittany, Rhône-Alpes and Midi-Pyrénées are also regions in which biotech firms set up. Firms specialising in genome and drug-development technologies are situated primarily in Ile de France, while firms in Aquitaine, Brittany and Auvergne focus more on agri-food related markets. The regions with the highest proportion of new firms are Auvergne, Rhône-Alpes and Ile de France, while firms in Alsace, Brittany and Centre are generally older. A degree of regional specialisation, sometimes very small, emerges, especially around pharmaceutical and genome related technologies[5] in Ile de France and around agrofood related markets in Auvergne, Aquitaine and Brittany.

The new public policy enables the creation of a large number of diverse biotech firms. They target mainly industries (agriculture, agrofood, health and other industries involved in life sciences) to sell their products or services. The core competencies of the firm describe the products and services that it designs, produces and markets. Four categories have been identified:

- Product development (20%). The firm's business is production and marketing of products. It does not produce customised products only; it also mass-produces.
- Diagnosis and creation of tests and/or biological material (55%). These firms develop two complementary activities: a) as service providers to other companies they create tests, biological material with specific characteristics, and customised diagnoses; and b) they design, produce and commercialise diagnostic kits, either directly or through other companies.
- Design and production of equipment and material for laboratories (9%). These firms cater for all sectors.
- Development aid methods or sequencing. These firms (17 %) design methods enabling firms to improve their processes or to market their products more effectively (e.g. CRO[6]). They cater primarily for the pharmaceutical and agrofood sectors.

To sum up, out of the 150 firms active in the human health sector, few are directly engaged in the production of drugs. Firms in the agriculture, agrofood or environment fields produce mainly seeds or foods with specific features (health or functional food). Service firms in these sectors mainly provide tests or diagnostic kits. SMEs focused on the cosmetic or animal health sectors have largely the same characteristics: close to firms in the human health field, they develop products or services, which do

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[5] When comparing France, U.K. and Germany biotech specialisation, Lemarié, Delooze and Mangematin. (2000) confirm that specialisation can be defined by the couple targeted market and technologies.

not require specific marketing licenses. This market positioning often corresponds to a strategy for progressively conquering the human health market.
Firms active in all the sectors are mainly those, which design and develop generic tools or methods (such as sequencing or instrumentation).

In biotechnology, the prevailing role of the French SMEs started to be recognised both as a « scientific gate keeper » translating knowledge into usable and marketable technology for other firms, and as a strategic partner in co-operation in the R&D and production stage with large firms to create innovation: pharma companies ensure that they access the relevant technologies to their own discovery capabilities through strategic alliances. The public policy makers and the companies have integrated the institutional dimension of technology transfer and diffusion mechanisms between institutions producing knowledge, small companies producing skills and industries producing industrial development, the fruit of converging strategies (comparable results with Casper 1999).
So the public authorities commitment to promoting programs and the improvement of the overall institutional framework have stimulated the creation of some twenty new companies in 1999. But their sustainability and their future depend on their technology strategies. Survival for innovative SMEs requires pursuing a technology-deepening strategy, but the market is limited for their earlier products. The lack of sufficient funds prevents the early stage biotech companies to investigate new projects outside their assets of competencies. So SMEs are often forced to develop a technology-widening strategy, including becoming technology or services providers. Indeed, there are very few SMEs that achieve a critical size and profitability without relying on major pharmaceutical groups.

CONCLUSION

Despite of the sporadic and discontinuous strategy of the State action in S&T policy in France, during the decade 1985-1996, a decisive prerequisite has been laid down for the creation of a space of innovation in genomics and biotechnologies. Major instruments for inducing the change have been developed by the public authorities, so at the state level as at the local level: they organised interaction between universities and research, small enterprises, large firms, and financial funds, as a major component of the innovation process, particularly through the establishment of intermediate institutions with a spatial dimension (Lundvall, 1993, Lemarie *et al.*, 2001).
This new stronger decentralised policy is more relevant to the specific innovation structure in biotech, in which a large extent knowledge is locally generated: both the spatial concentration of scientific and technological activities and the initial networks of the entrepreneur (often from the public or private research community) compound a dynamic scientific environment suited to the emergence of new biotech activities, at the time of creation.

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[6] Consultancy research organisation

But the sector is not yet consolidated the problem of firm's survival after a two or three years period is a very real one in an industry characterised by a fast technological change. As the firms grow, organisational proximity dominates, and an international profile has to emerge. In France there is a great diversity in the biotech SMEs trajectories, adapted to the projects of their creators or shareholders, and becoming a world leader in its « niche » of specialisation and in the stock market is not the only path to « success ». It is likely that from their creation, firms condition their future and growth trajectory, depending on the amount of initial investments, the networks they fit into, the partnerships they form and their appeal, or not, to outside investors.

On the institutional level, public policy interventions in favour of business creation seem to combine more harmoniously with non-for profit organisations'ones, but the maintaining of mission-oriented elements in the new schemes raises the risk that the State replaces initiatives by the main protagonists in the science-industry partnerships, which are beginning to proliferate under the favourable influence of general diffusion-oriented measures. Policies supporting innovation and high-tech SMEs have to take into account this new dimension, the proliferation and the variety of the players and the diversity of the firms' viability.

The stages of an innovation process are not linear; rather, they overlap and interpenetrate, producing a "cumulative irreversibility" because of incremental innovations. In spite of the present combination of partially contradictory institutional schemes for the development of a biotechnology sector, France has thus entered an institutional learning process.

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